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Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana: a posttrial observational analysis

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Abstract

Objective—Thirty-six months of isoniazid preventive therapy (36IPT) was superior to 6 months of IPT (6IPT) in preventing tuberculosis (TB) among HIV-infected adults in Botswana. We assessed the posttrial durability of this benefit.

Design—A 36-month double-blind placebo controlled trial (1 : 1 randomization) with recruitment between November 2004 and July 2006 and observation until June 2011.

Methods—One thousand, nine hundred and ninety-five participants were followed in eight public health clinics. Twenty-four percent had a tuberculin skin test ≥5 mm (TST-positive). A minimum $CD4^+$ lymphocyte count was not required for enrolment. Antiretroviral therapy (ART) was provided in accordance with Botswana guidelines; 72% of participants retained by June 2011 had initiated ART. Multivariable analysis using Cox regression analysis included treatment arm, TST status, ART as a time-dependent variable and $CD4^+$ cell count at baseline and updated at 36 months.

Results—In the posttrial period, 2.13 and 2.14 per 100 person-years accumulated, whereas 0.93 and 1.13% TB incidence rates were observed in the 36IPT and 6IPT arms, respectively ($P = 0.52$). The crude hazard ratio of TB during the trial and posttrial was 0.57 [95% confidence intervals (CI) 0.33, 0.99] and 0.82 (95% CI 0.46, 1.49), and when restricted to TST-positive participants was 0.26 (95% CI 0.08, 0.80) and 0.40 (95% CI 0.15, 1.08), respectively. Multivariable analysis

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Supplementary Digital Content: one Word document consisting of tables and figures, http://links.lww.com/QAD/A611.

Conflicts of interest

The authors have no conflicts of interest to declare.

showed that ART use was associated with reduced death (adjusted hazard ratio 0.36, 95% CI 0.17–0.75) but not TB (0.92, 95% CI 0.55–1.53) in the posttrial period.

Conclusion—The benefit of 36IPT for TB prevention declined posttrial in this cohort. Adjunctive measures are warranted to prevent TB among HIV-infected persons receiving long-term ART in TB-endemic settings.

Keywords

antiretroviral therapy; HIV; isoniazid; preventive therapy; tuberculin; tuberculosis

Introduction

Antiretroviral therapy (ART) reduces the risk of tuberculosis (TB) in HIV-infected persons [1]. Botswana, a country in which 18% of the population is infected with HIV and had a TB notification rate exceeding 500 cases per 100 000 population between 1999 and 2009, launched a national ART programme in 2002 and by 2008 reached over 90% of its target population [2]. However, long-term cohorts in ART programmes in sub-Saharan Africa report 1–5% per annum TB rates [3–6]. In such settings, ART alone is insufficient to reduce incident TB in HIV-infected persons [7].

Isoniazid preventive therapy (IPT) prevents TB in tuberculin skin test (TST) positive HIV-infected persons, and countries that have adopted IPT as policy have selected 6–9 month regimens. As recommended by the WHO, in 2002 the Botswana government launched a national IPT programme in which it provided 6 months IPT (6IPT) to all HIV-infected persons without requiring a TST [8]. In two settings where clinical trials had demonstrated the efficacy of 6IPTand where posttrial TB incidence was investigated, the benefit of IPT was lost within 6–18 months [9,10]. This lack of durability of 6IPT led us to conduct a randomized, double-blind, placebo-controlled trial in HIV-infected persons in Botswana to assess the benefit of 36IPT [11]. We concluded that compared with 6IPT, 36 months' IPT (36IPT) reduced TB by 43% in all participants. However, this benefit was limited to TST-positive 36IPT recipients in whom there was a 74% reduction in TB and a 68% reduction in mortality compared with TST-positive 6IPT recipients. Multivariable analysis demonstrated an additional reduction in TB attributable to ART. Such a dual benefit of ARTand IPT had also been reported from retrospective studies of programmes in Brazil and South Africa [12,13].

The duration of the benefit of 36IPT after cessation of prophylaxis in HIV-infected persons with ready access to ART is not known. We now report on TB incidence and mortality in the Botswana cohort after scheduled cessation of IPT and in the posttrial period.

Methods

Potential participants were screened at eight public health clinics in Gaborone and Francistown, Botswana, where government IPT and ART programmes were operated. Typically, participants were recently diagnosed with HIV infection. Persons over the age of 18 were enrolled into the IPT trial between 26 November 2004 and 20 July 2006. A detailed

description of the study's design, methods and results are published [11]. Potential participants with any $CD4^+$ lymphocyte count or TST status were eligible for inclusion. Reasons for exclusion included cough, weight loss, night sweats, other acute illnesses, previous IPT, TB treatment within the previous 3 years, neutrophil count below 1000 cells/ml, or an abnormal chest radiograph without antecedent TB or pneumonia [14]. Enrolled participants were randomly assigned 1 : 1 to the 6IPT or 36IPT arm; randomization was performed with the use of random, permuted blocks of 10. On a monthly basis, participants received open-labeled isoniazid for 6 months to be taken daily at a dose of 300 mg for weight 30–49 kg and 400 mg for weight ≥ 50 kg supplemented with 25 mg of pyridoxine. In late 2005 the national guidelines changed and beginning 1 January 2006, all study participants were provided 300 mg daily. Participants self-administered study drug were followed-up monthly during the trial at which time they were asked about TB symptoms, and if asymptomatic received another month's supply of the study drug. In the posttrial period, participants received no more study drug and were evaluated at quarterly visits in the same manner as during the trial until 30 June 2011.

ART was offered according to Botswana national guidelines for participants with $CD4^+$ lymphocyte counts below 200 cells/μl or WHO clinical stage 3 or 4 disease. In 2009, this guideline changed to include individuals with $CD4^+$ cell count below 350 cells/μl. ART regimens were almost entirely zidovudine, lamivudine, and either nevirapine or efavirenz.

At enrolment, we performed TST by placing five tuberculin units (0.1 ml) of purified protein derivative (RT/23 Statens Serum Institut, Copenhagen, Denmark) intradermally; the reaction was read by study nurses within 48–72 h. Induration at least 5 mm was regarded as positive.

Study endpoints before the end date were either incident TB or death from any cause. We assessed participants with cough of any duration, weight loss, nocturnal sweats, or lymphadenopathy for incident TB and took sputum samples or biopsy specimens for microscopy and mycobacterial culture. The primary endpoint was incident TB (definite, probable, and possible TB) and the secondary endpoint was death. Incident TB was defined as a clinical presentation consistent with TB and response to anti-TB therapy. Incident disease was categorized as definite if one or more cultures were positive for mycobacteria and speciated as *Mycobacterium tuberculosis* complex or if two or more sputum smears were positive for acid-fast bacilli; probable if one sputum smear or one biopsy specimen was positive for acid-fast bacilli; and possible if smears and cultures were negative or not done.

Statistical analysis

Analyses comparing the incidence of TB in the two arms were conducted in four periods: during the trial; during the trial and posttrial; after scheduled completion of IPT, that is, after month 6 in the 6IPTarm and after month 36 in the 36IPT arm; and posttrial. In each period, we applied Cox regression analyses to the intent-to-treat cohort to determine hazard ratios (HRs) comparing 6IPT and 36IPT arms; $P < 0.05$ was regarded as significant. Participants with both $CD4^+$ cell counts and TST at baseline were included in multivariable analyses. Duration of ART was defined as the number of days from initiation to the endpoint (or date of study completion) minus 60 days. This 60-day rule was applied because in five instances clinicians suspected AIDS progression rather than TB and so had initiated ART before anti-

TB therapy. Our intent being to examine the preventive effect of ARTon TB or death, we discounted previous ART for these five TB cases. Multivariable predictive Cox regression models were used to assess the effect of treatment arm on the incidence of TB or death during the aforementioned periods. We initially included treatment arm, baseline $CD4^+$ lymphocyte count as a binary variable (cutoff 200 cells/μl), baseline TST, ART as a time-dependent variable, and interaction terms in the models (P <0.05 significance level for included interaction terms). Without prespecified stopping rules, we applied both backward and forward model selection procedures with all interaction terms. ARTwas treated as a continuous variable in the model and estimates for the effect of ART were derived after 360 days' use and compared with participants who never initiated ART. Updated $CD4^+$ cell counts taken at 36 months ± 3 months into the period of observation were introduced in the multivariable models for any period extending beyond 36 months. Statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Ethics

All participants provided signed informed consent forms and received transportation reimbursements. The protocol was approved by the Botswana Human Research Development Committee and the US Centers for Disease Control and Prevention institutional review board. The trial is registered at ClinicalTrials.gov, number NCT00164281.

The US Centers for Disease Control and the US Agency for International Development funded the study, but had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The number of persons screened, reasons for exclusion, and participants enrolled in the study are shown in Fig. 1. At enrolment 72% (1436/1995) of participants were female, their median age was 32 years, median $CD4^+$ cell count was 297 cells/μl. TST was available for 1919 participants of whom 24% were TST-positive. The treatment arms were balanced in terms of demographic factors for the 36-month trial [11]. For analyses in the posttrial and after IPT periods, the arms were also balanced with the exception of somewhat more participants being underweight at baseline in the 6IPT arm compared with the 36IPT arm and, expectedly during the after-IPT period, more participants in the 36IPT arm having initiated ART (Supplementary Table 1, http://links.lww.com/QAD/A611).

ART had been initiated in 2% of participants at enrolment which increased to 47% by the end of the 36-month trial and 72% among participants retained by the end of observation on 30 June 2011, and was evenly distributed by study arm (Fig. 2). The 1678 participants who agreed to remain under observation after the trial accumulated a median of 2.8 years of observation. In the posttrial period 2130 person-years of observation were accrued by participants in the 6IPT arm (n = 827) and 2142 in the 36IPT arm (n = 851); among the 468 who were TST-positive, person-years accrued were 891 and 913, respectively. The median $CD4^+$ cell count of the cohort was estimated to be 432 cells/μl (interquartile range 320–562)

among those remaining under observation at 6 years (Fig. 2). Accumulated time on ART in the cohort totaled 4464 person-years.

Endpoints

A total of 98 incident TB cases were observed: 53 (54%), 17 (17%), and 28 (29%) were definite, probable and possible, respectively. In the 6IPT and 36IPT arms, TB rates were 1.3 per 100 person-years (%) and 0.7% during the trial ($P = 0.047$) and 1.1 and 0.9% posttrial ($P = 0.52$), respectively. Limited to TST-positive participants, TB rates were 2.2 and 0.6% during the trial ($P = 0.02$) and 1.3 and 0.7% posttrial ($P = 0.07$) in the 6IPTand 36IPTarms, respectively. Among TST-negative participants, TB rates were 1.0 and 0.8% during the trial ($P = 0.40$) and 0.9 and 1.1% posttrial ($P = 0.50$) in the 6IPT and 36IPT arms, respectively (Table 1). Anti-TB drug susceptibility data were available for 83% (44/53) of definite TB cases. Four cases and one case of isoniazid-resistant TB were detected in the 6IPT and 36IPT arms, respectively. One case of multidrug-resistant TB (defined as both isoniazid and rifampin resistance) was detected in each arm.

A total of 106 deaths were observed. In the 6IPT and 36IPT arms, death rates were 1.4% in both arms during the trial and 0.6 and 0.7% posttrial, respectively; limited to the TST-positive cohort, death rates were 2.2 and 0.7% during the trial, and 0.6 and 0.4% posttrial, respectively.

Efficacy of 36IPT vs. 6IPT in the prevention of tuberculosis and death

TST-positive participants who were the chief beneficiaries of 36IPT during the trial experienced a 60–74% reduction in TB during all four periods analyzed, particularly when restricted to those who were at least 80% adherent by medication pickup (Table 1). A waning effect of 36IPT's efficacy was evident with accumulated time after IPT: HR 0.26 [95% confidence intervals (CI) 0.08–0.80] during the trial, 0.33 (95% CI 0.16–0.68) during and after the trial and 0.40 (95% CI 0.15–1.08) posttrial. TB incidence was highest in the first year after 36IPT but subsequently declined (Fig. 3a and b). When combining TST-positive and TST-negative participants, 36IPT recipients experienced marginally significant reductions in TB in the periods during and after the trial (HR 0.68, $P = 0.057$) (Fig. 3C) and after IPT (HR 0.64, $P = 0.100$), but had no residual benefit in the posttrial period (HR 0.82, $P = 0.52$, Supplementary Figure 3A, http://links.lww.com/QAD/A611). Compared with the 6IPTarm, 36IPT did not reduce the risk of death in the whole cohort but TST-positive participants receiving 36IPT experienced a reduction in death after IPT (HR 0.37, $P = 0.088$) and during and after the trial (HR 0.41, $P = 0.028$).

Multivariable analysis of the impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis and death

Baseline $CD4^+$ cell count and TST data were available for 1919 participants and updated (36 month) $CD4^+$ cell counts were available for 1391 participants. Adjusting for ART did not modify the effect of IPTon TB or death in any period analyzed and the interaction between TSTand treatment arm remained significant in all these periods. In comparison to participants who did not receive ART, 360 days' use of ARTreduced the adjusted hazard ratio (aHR) of TB by 47% during the trial [aHR 0.53 (95% CI 0.31–0.91)] but not in

subsequent periods (Table 2). Compared with $CD4^+$ cell count below 200 cells/μl, having a $CD4^+$ cell count at least 200 cells/μl was associated with a reduced adjusted hazard of TB by 41% during and after the trial [aHR 0.59 (95% CI 0.36–0.97)] but not posttrial [aHR 0.85 (95% CI 0.39–1.83)]. By contrast, 360 days of ART receipt reduced the hazard of death in all periods analyzed although during the trial only among those with $CD4^+$ count below 200 cells/μl [aHR 0.40 (95% CI 0.23–0.70)]. Furthermore, a $CD4^+$ cell count of at least 200 cells/μl was associated with a decline in death during and after the trial [aHR 0.37 (95% CI 0.24–0.57)], posttrial [aHR 0.26 (95% CI 0.09–0.71)] as well as in the period after IPT [aHR 0.53 (95% CI 0.28–1.03)].

Discussion

Whereas the efficacy of 36IPT for incident TB was no longer statistically significant among all participants after IPT, TST-positive participants experienced a durable –although waning – benefit during the years following treatment. From the only other African (Soweto, South Africa) trial to compare 6IPT against a continuous IPT regimen, authors reported that the TB rate ‘escalated markedly after discontinuation’ of continuous isoniazid (actually provided a median of 3.3 years) among TST-positive HIV-infected participants [15]. We too observed a rapid accumulation of TB cases in the first year following 36IPT (Fig. 3b and c), although this increase was insufficient to substantively diminish the overall durability of 36IPT among TST-positive participants. TST-negative participants had no statistically significant benefit from 36IPT during or after the trial.

In the absence of additional studies of TB incidence among HIV-infected patients after receipt of at least 3 years of IPT, an examination of outcomes after shorter courses of IPT are informative. Researchers conducting isoniazid chemoprophylaxis trials either with or without ART provision, observed steady and high rates of TB within 6–18 months after 6IPT [9,10,16,17]. Researchers conducting the THRio trial in Brazil, a moderate TB-incidence setting, have presented TB incidence data after 6IPT among TST-positive clinic patients most of whom were receiving ART [16]. They observed that TB risk was ‘concentrated within one year of stopping IPT then remained constant’ and suggested that this higher risk was largely from participants who did not complete chemoprophylaxis. We previously reported a similar increase in TB after 6IPT (Supplementary Figure 3B, http://links.lww.com/QAD/A611) as was observed in the 6IPT arm of the Soweto trial [11,15]. Therefore, in general it appears that within the first year of IPT–whether a 6 or 36-month course – a subpopulation of HIV-infected participants in these moderate-to-high incidence settings experience TB disease; the majority of treated patients experience a steady but lower rate of TB after the first year of IPT. Whether the incident TB cases after IPT represent a failure to sterilize the latent infection present at the time of IPT initiation or reinfection is unclear but may be a function of TB-endemicity. Authors of a recently published trial conducted in South African gold mines observed a more than doubling of TB incidence almost immediately after a 9 month course of IPT and attributed it to the intense infection pressure of this environment [18]. By contrast, an IPT trial conducted among TST-positive HIV-infected participants mostly from the United States – a nonendemic setting – showed a more than 4-year durability of 12 months’ IPT [19].

The persisting survival benefit among TST-positive HIV-infected participants associated with 36IPT after IPT is a unique but no longer a surprising finding in programmes where ART is also provided. Although not universally detected, several studies have shown improved survival among IPT recipients: completion of 6IPTwas associated with a 60% reduction in mortality in a Tanzanian cohort of TST-positive HIV-infected participants with baseline $CD4^+$ cell count at least 200 cells/μl and with access to ART [20]; a retrospective analysis of South African miners initiating ART showed that 6IPT reduced their risk of death by 66% [21]. The Soweto IPT trial observed the lowest rate of 'death or TB' in TST-positive HIV-infected participants receiving 36IPT [15]. The THRio study observed reduced rates of 'TB and death' among HIV-infected adults in ART clinics among whom 6IPT was provided to TST-positive participants [22]. As previous meta-analyses and a recently concluded randomized trial of 12 months of IPT among ART recipients did not observe a mortality benefit, some insights about the varied survival benefit of IPT have been proposed but further study will be needed [23–25].

The other intervention known to strongly prevent TB in HIV-infected persons that was introduced in an uncontrolled fashion in our study was ART. We did not observe a statistical interaction between ARTand IPT but found that IPT and ART were both TB protective during the trial period. Although ART or its associated immune reconstitution did not play a substantial role in TB prevention after IPT, it was death that ART impacted: there were almost 50% more TB cases than deaths after the trial ended. Our observation that ARTand $CD4^+$ cell count at least 200 cells/μl prevent death throughout the approximately 6-year period is consistent with numerous studies in many settings. Our finding that ART impacted TB only in the first 3 years of the trial is also consistent with what has thus far been published about the long-term use of ART in TB-endemic settings: after a steep decline in the first year, TB incidence settles at a rate above that of HIV-uninfected persons [4,5,26]. Few multiyear studies of TB incidence among HIV-infected persons receiving ART have incorporated updated $CD4^+$ cell counts in multivariable analyses. Two such studies found incident TB to be more strongly associated with updated $CD4^+$ cell counts than merely the duration of ARTuse [26,27]. While we found such an association for death, we did not find a statistically significant association of updated $CD4^+$ cell count with incident TB. Nevertheless, our analysis is unique as it examines the effect on incident TB of ART initiation at variable points in time, updated $CD4^+$ cell counts at the 3-year time point and incorporates the effect of long-term isoniazid prophylaxis during almost 6 years of observation.

A limitation of our study is that we may not have been able to accurately assess the effect of immune recovery on incident TB as might have been possible with quarterly $CD4^+$ cell counts in all participants. Additionally, there is potential bias in the comparison of TB and death in the two arms during the after-IPT period because the comparison does not include participants as randomized at enrolment. Strengths of our study include a prospectively followed cohort, more than 50% bacteriologic confirmation of TB cases, endpoints that were confirmed by an independent endpoints committee, and conservative modeling of treatment effects. As the use of ARTwas not controlled in our study's design, the strength of our conclusions for ART is much the same as that for observational cohorts.

It is possible that we would have observed a lower TB incidence in the cohort had ART been initiated at higher $CD4^+$ cell counts than 200–250 cells/μl. Nevertheless, TB rates remain unacceptably high in TB-endemic settings despite earlier provision of ART: among participants of a multicountry randomized trial who initiated ART at a median $CD4^+$ cell count of 428 cells/μl, the TB rate was 0.9% per year, which is quite similar to other studies in such settings and in populations initiating ART at lower $CD4^+$ cell counts [28]. The additive benefit of IPT to ART has now been confirmed in a randomized placebo-controlled trial among adults in Cape Town receiving ART: 12 months of IPT led to a 37% reduction in TB [24]. This randomized controlled trial, combined with observational analyses from ART programmes in Brazil, South Africa, Hong Kong, Spain, Thailand, and Botswana, strengthen the biologically plausible notion that together and through different mechanisms of action, ART and IPT better prevent TB [12,13,29–31]. Taken together, these data affirm the importance of implementing the WHO's recommendations by scaling up IPT for HIV-infected persons. Additionally, more potent and durable regimens are urgently needed to prevent TB disease in HIV-infected persons living in TB-endemic settings.

In conclusion, the TB prevention benefit of 36IPT as compared with 6IPT declined after IPT in a cohort of HIV-infected persons living in a TB-endemic setting despite ready access to ART. The 36IPT's effect was durable among TST-positive participants but had a diminished efficacy with the passage of time. Although initiation of ART at $CD4^+$ cell counts above 350 cells/μl will benefit HIV-infected persons and their HIV-uninfected sexual partners, TB incidence remains high in the long-term for those living in TB-endemic settings and adjunctive measures for TB prevention – possibly including continuous IPT – are warranted.

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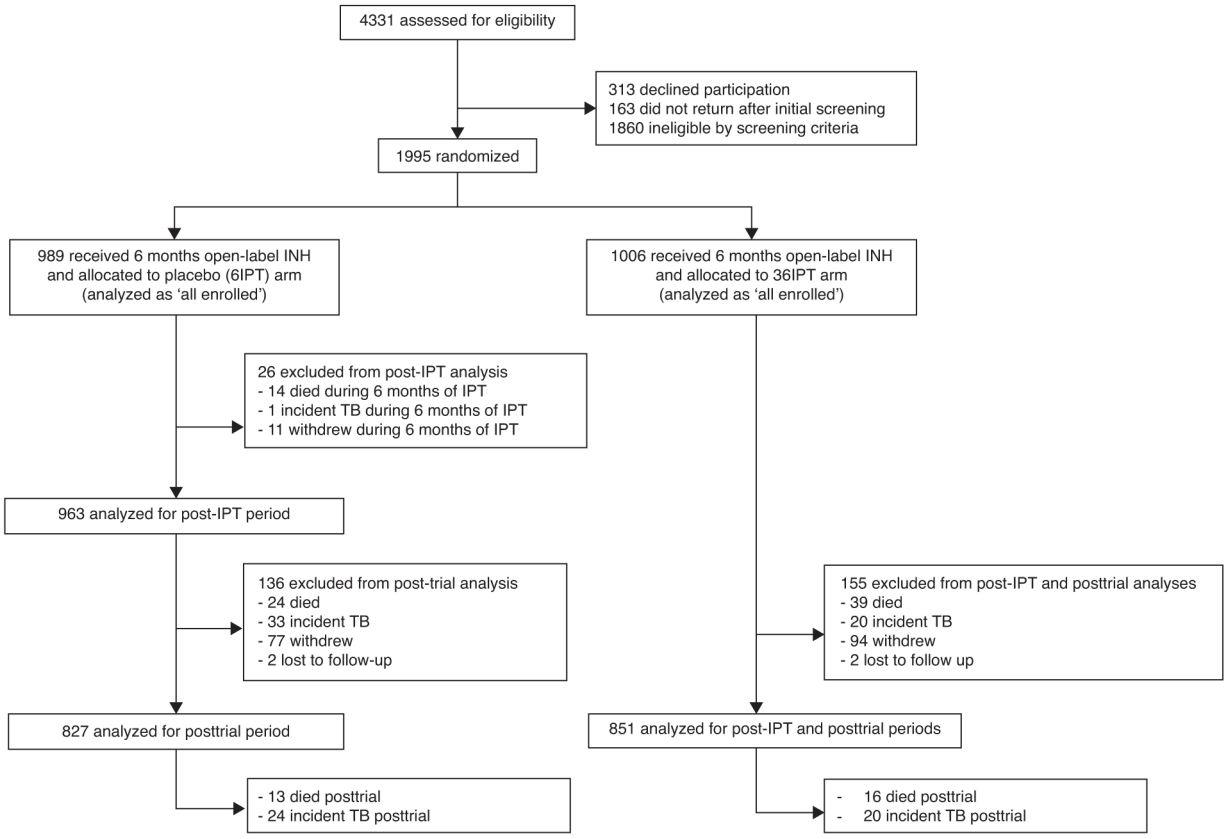
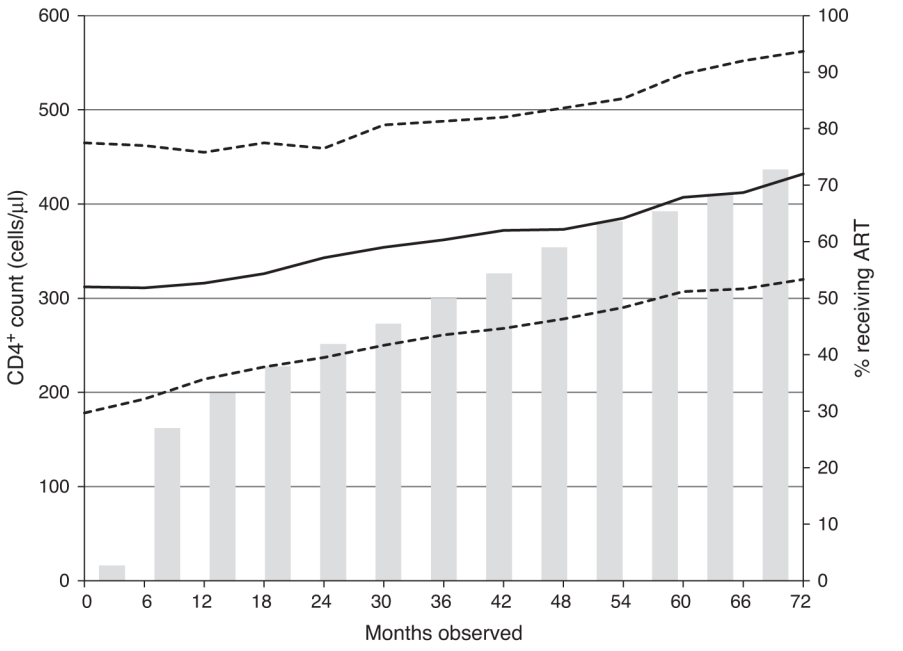


Fig. 1. Trial analysis profile

36IPT, 36 months of isoniazid preventive therapy; 6IPT, 6 months of isoniazid preventive therapy followed by 36 months of placebo; INH, isoniazid; IPT, isoniazid preventive therapy; TB, tuberculosis.



Month observed	0	6	12	18	24	30	36	42	48	54	60	66	72
Number at start of month	1995	1946	1873	1815	1760	1718	1684	1628	1587	1520	1403	1084	1398

Fig. 2. Cumulative initiation of antiretroviral therapy (ART) and median CD4$^+$ lymphocyte count of the cohort

The gray bars shows the cumulative proportion of participants at the beginning of each preceding half-year who had initiated ART. The solid line represents the median CD4$^+$ lymphocyte count of the entire cohort with 25th and 75th percentiles shown in dashed lines.

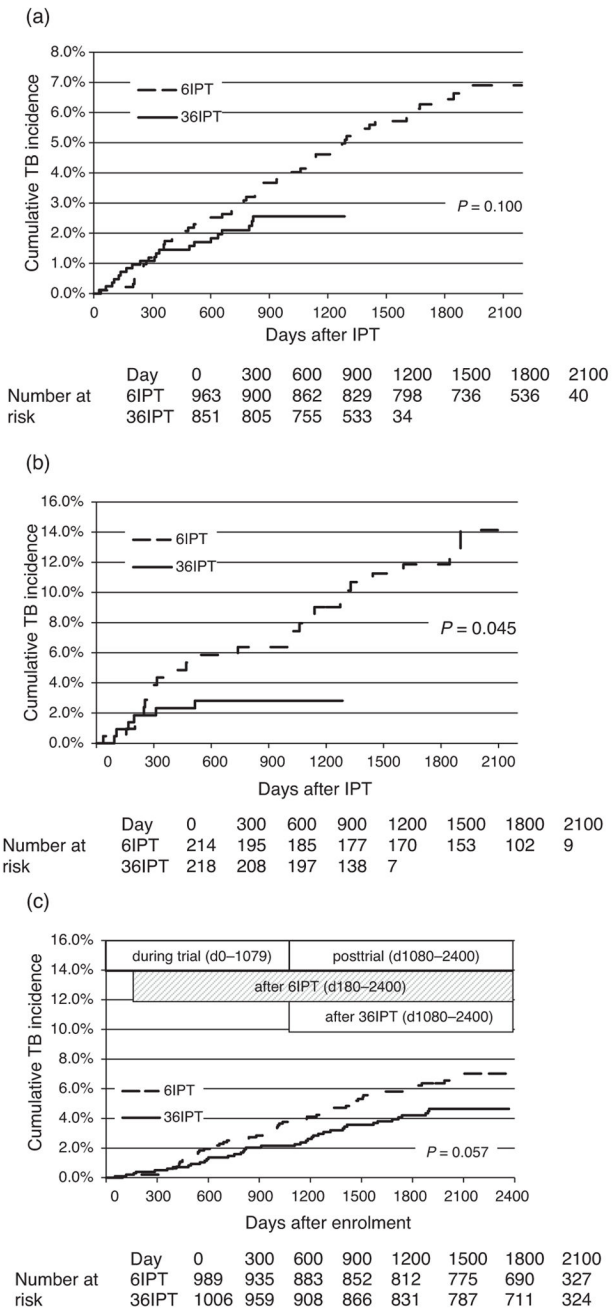


Fig. 3. Cumulative tuberculosis incidence among participants (a) after scheduled IPT, (b) after scheduled IPT restricted to those who were TST-positive, (c) during and after the 36-month trial

36IPT, 36 months of isoniazid preventive therapy; 6IPT, 6 months of isoniazid preventive therapy followed by 36 months of placebo; IPT, isoniazid preventive therapy; TST, tuberculin skin test.

Table 1

Crude hazard ratio of incident tuberculosis and death by treatment arm and period of observation.

	Trial period		Trial and posttrial period		Posttrial period (i.e., post month 36)		After scheduled IPT (i.e., post month 6 for 6IPT and post month 36 for 36IPT)	
	6IPT *n* = 989	**36IPT *n* = 1006**	**6IPT *n* = 989**	**36IPT *n* = 1006**	**6IPT *n* = 827**	**36IPT *n* = 851**	**6IPT *n* = 963**	**36IPT *n* = 851**
100 person-years	26.9	27.7	48.2	49.1	21.3	21.4	43.3	21.4
TB cases[§]	34	20	58	40	24	20	57	20
All	0.57 (0.33, 0.99)		0.68 (0.45, 1.01)		0.82 (0.46, 1.49)		0.64 (0.37, 1.09)	
(HR, 95% CI)	$P = 0.047^{*}$		$P = 0.057$		$P = 0.52$		$P = 0.10^{\dagger}$	
TST-positive	0.26 (0.08, 0.80)		0.33 (0.16, 0.68)		0.40 (0.15, 1.08)		0.38 (0.15, 0.98)	
(HR, 95% CI)	$P = 0.02^{*}$		$P = 0.003^{*}$		$P = 0.07^{\dagger}$		$P = 0.045^{*,\dagger}$	
TST-negative	0.75 (0.38, 1.46)		0.94 (0.56, 1.55)		1.31 (0.60, 2.89)		0.84 (0.43, 1.65)	
(HR, 95% CI)	$P = 0.40$		$P = 0.80$		$P = 0.50$		$P = 0.61$	
Deaths[§]	38	39	51	55	13	16	37	16
All	1.00 (0.64, 1.56)		1.06 (0.72, 1.55)		1.23 (0.59, 2.56)		0.79 (0.42, 1.48)	
(HR, 95% CI)	$P = 1.0$		$P = 0.77$		$P = 0.58$		$P = 0.56^{\dagger}$	
TST-positive	0.32 (0.11, 0.90)		0.41 (0.18, 0.91)		0.62 (0.17, 2.32)		0.37 (0.12, 1.16)	
(HR, 95% CI)	$P = 0.031^{*}$		$P = 0.028^{*}$		$P = 0.48$		$P = 0.088^{\dagger}$	
TST-negative	1.28 (0.76, 2.15)		1.32 (0.84, 2.07)		1.44 (0.58, 3.57)		1.02 (0.46, 2.28)	
(HR, 95% CI)	$P = 0.36$		$P = 0.24$		$P = 0.44$		$P = 0.96$	

6IPT, 6 months of isoniazid preventive therapy followed by 36 months of placebo; 36IPT, 36 months of isoniazid preventive therapy; CI, confidence interval; HR, hazard ratio; TST, tuberculin skin test.

[*] P <0.05.

[†] P <0.05 when the analysis was restricted to participants who were ≥80% adherent by medication pickup during the 36-month trial (see Supplementary Appendix, http://links.lww.com/QAD/A611).

[§] Numbers of TB cases and deaths in TST-positive and TST-negative participants are shown in supplementary Table 2, http://links.lww.com/QAD/A611.

Table 2

Multivariable adjusted hazard ratios for incident tuberculosis and death by analytic period.

	Interacting strata	Trial (*n* = 1891)	Trial and posttrial (*n* = 1919)	Posttrial (*n* = 1587)	After scheduled IPT (*n* = 1743)
Tuberculosis					
Variables included 36IPT vs. 6IPT		A,T,C,R,A*T	A,T,A*T	A,T,C,A*T	A,T,A*T
	TST-positive	0.26 (0.09, 0.80)†	0.33 (0.16, 0.69)†	0.40 (0.15, 1.08)§	0.38 (0.15, 0.94))†,§
	TST-negative	0.88 (0.44, 1.76)	1.04 (0.62, 1.74)	1.30 (0.59, 2.87)	1.00 (0.51, 1.96)
ART360 vs. ART 0		0.53 (0.31, 0.91)†	0.90 (0.77, 1.04)	0.92 (0.55, 1.53)	0.97 (0.78, 1.19)
$CD4^+$ ≥200 cells/μl vs. $CD4^+$ <200 cells/μl		0.47 (0.22, 1.02)	0.59 (0.36, 0.97)†	0.85 (0.39, 1.83)	0.93 (0.52, 1.67)
Death					
Variables included 36IPT vs. 6IPT		A,T,C,R,A*T,C*R	A,T,C,R,A*T,C*R	A,T,C,R,A*T	A,T,C,R,A*T
	TST-positive	0.34 (0.12, 0.94)†	0.43 (0.20, 0.97)†	0.63 (0.17, 2.34)	0.40 (0.13, 1.23)§
	TST-negative	1.26 (0.75, 2.13)	1.30 (0.83, 2.04)	1.44 (0.58, 3.58)	0.98 (0.46, 2.12)
ART360 vs. ART 0			0.78 (0.66, 0.93)†	0.36 (0.17, 0.75)†	0.78 (0.60, 1.02)
	$CD4^+$ ≥200 cells/μl	1.11 (0.77, 1.59)			
	$CD4^+$ <200 cells/μl	0.40 (0.23, 0.70)†			
$CD4^+$ ≥200 cells/μl vs. $CD4^+$ <200 cells/μl			0.37 (0.24, 0.57)†	0.26 (0.09, 0.71)†	0.53 (0.28, 1.03)
	ART360	0.70 (0.38, 1.29)			
	ART 0	0.25 (0.14, 0.44)†			

Numbers included in analyses are fewer than those in Table 1 because of missing baseline TSTs and/or $CD4^+$ cell counts. The $CD4^+$ cell count variable was dichotomized at the 200 cells/μl cutoff and treated as a time-varying covariate that was updated at month 36. ART was introduced as a time-dependent variable at the time of initiation. 6IPT, 6 months of isoniazid preventive therapy; 36IPT, 6 months of isoniazid preventive therapy; A, treatment arm (6IPT vs. 36IPT); A*T, interaction term between treatment arm and TST; ART 0, provision of no antiretroviral therapy; ART360, provision of antiretroviral therapy for 360 days; C*R, interaction term between $CD4^+$ ≥or <200 cells/μl and antiretroviral therapy; C, $CD4^+$ ≥200 cells/μl vs. $CD4^+$ <200 cells/μl; IPT, isoniazid preventive therapy; R, antiretroviral therapy; T, TST; TST, tuberculin skin test.

† P <0.05.

§ P <0.05 when the analysis was restricted to participants who were ≥80% adherent by medication pickup during the 36-month trial (see Supplementary Appendix, http://links.lww.com/QAD/A611).